CLAIMS

1. A controlled-release pharmaceutical formulation comprising a phosphodiesterase type 4D (PDE4D) inhibitor, or a pharmaceutically acceptable salt thereof, said formulation exhibiting at least one of the following characteristics:

(i) a T_{max} of greater than about 1.5 hours when dosed *in vivo*;

(ii) less than about 80% of said PDE4D inhibitor, or said pharmaceutically acceptable salt thereof, is released *in vivo* at about 1.5 hours;

(iii) less than about 80% of said PDE4D inhibitor, or said pharmaceutically acceptable salt thereof, is released *in vitro* at about 1.5 hours;

(iv) an *in vitro* delivery lag time prior to initiation of release of said PDE4D inhibitor, or said pharmaceutically acceptable salt thereof, of between 0.5 hours and about four hours;

(v) an *in vivo* delivery lag time prior to initiation of release of said PDE4D inhibitor, or said pharmaceutically acceptable salt thereof, of between 0.5 hours and about four hours.

2. A controlled-release formulation of claim 1, wherein said PDE4D inhibitor comprises (R)-2-[4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid, or a pharmaceutically acceptable salt thereof, or 2-(4-fluorophenoxy)-N-[4-(1-hydroxy-1-methyl-ethyl)-benzyl]-nicotinamide, or a pharmaceutically acceptable salt thereof.

3. A controlled-release pharmaceutical formulation of claim 1 comprising a core, and a coating around said core, wherein:

(a) said core comprises a drug-containing composition and a water-swellable composition, each occupying essentially separate regions within said core;

(b) said drug-containing composition comprises a PDE4D inhibitor, or a pharmaceutically acceptable salt thereof, and a drug-entraining agent;

(c) said water-swellable composition comprises a swelling agent; and

(d) said coating is water-permeable, water-insoluble, and has at least one delivery port therethrough.

4. A formulation of claim 3, wherein said PDE4D inhibitor comprises (R)-2-[4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid, or a pharmaceutically acceptable salt thereof, or 2-(4-fluorophenoxy)-N-[4-(1-hydroxy-1-methyl-ethyl)-benzyl]-nicotinamide, or a pharmaceutically acceptable salt thereof.

5. A formulation of claim 3, wherein said swelling agent of said water-swellable composition comprises an ionic or non-ionic polymeric swelling agent.

6. A formulation of claim 5, wherein said ionic polymeric swelling agent is selected from the group consisting of polacrilin potassium, polyacrilin resins, sodium alginate, sodium croscarmellose, and sodium starch glycolate; and said non-ionic polymeric swelling agent is selected from the group consisting of alginic acid, carboxymethylcellulose, hydroxypropylcellulose, microcrystalline cellulose, crospovidone, methylcellulose, polyethylene oxide, povidone, and starch.

7. A formulation of claim 6, wherein said swelling agent is selected from the group consisting of polyethylene oxide, sodium starch glycolate, and sodium croscarmellose.

8. A formulation of claim 3, wherein said water-swellable composition further comprises an osmotically effective agent.

9. A formulation of claim 3, wherein said water-swellable composition further comprises a tableting aid.

10. A formulation of claim 3, wherein the mass ratio of said drug-containing composition to said water-swellable composition has a value of at least 1.0, and said core has a strength following tableting of at least 3 Kp/cm^2.

11. A formulation of claim 3, wherein said coating has a water flux (40°/75% relative humidity) of at least 1.0 x 10^{-3} gm/cm^2 · hr, and a durability of at least 1 Kp/cm^2.

12. A formulation of claim 3, wherein said drug-containing composition further comprises a fluidizing agent, said fluidizing agent having a solubility of at least 30 mg/mL and comprising at least 10 wt% of said drug-containing composition.

13. A formulation of claim 12, wherein said fluidizing agent is selected from the group consisting of an organic acid, an organic base, and a sugar.

14. A formulation of claim 3, wherein said drug-containing composition further comprises a solubilizer.

15. A formulation of claim 14, wherein said solubilizer is selected from the group consisting of an organic acid, an organic base, an inorganic acid, an inorganic base, a surfactant, and a cyclodextrin.

16. A formulation of claim 3, wherein said drug-containing composition further comprises a concentration-enhancing polymer.

17. A formulation of claim 16, wherein said concentration-enhancing polymer selected from the group consisting of:

(a) ionizable cellulosic polymers;

(b) non-ionizable cellulosic polymers; and

(c) vinyl polymers and copolymers having substituents selected from the group consisting of hydroxyl, alkylacyloxy, and cyclicamido.

18. A formulation of claim 3, wherein said PDE4D inhibitor, or said pharmaceutically acceptable salt thereof, is in the form of a solid, amorphous dispersion.

19. A formulation of claim 18, wherein said solid, amorphous dispersion comprises a solid dispersion of said PDE4D inhibitor, or said pharmaceutically acceptable salt thereof, in a concentration-enhancing polymer.

20. A formulation of claim 3 wherein said PDE4D inhibitor comprises (R)-2-[4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid, or a pharmaceutically acceptable salt thereof; and wherein said swelling composition comprises between about 50% and about 75% w:w of the swelling layer being polyethylene oxide of a molecular weight (weight average) of between about 1,000,000 and about 7,000,000, and between about 25% and about 50% w:w of sodium chloride; and said drug composition comprises between about 0.5 and about 10% (w:w) of said drug, about 50% and about 70% of polyethylene oxide having a weight average molecular weight of between about 100,000 and about 600,000; and said coating comprises cellulose acetate and polyethylene glycol having a molecular weight (weight average) of between about 1,000 and about 10,000.

21. A formulation of claim 3 wherein said PDE4D inhibitor comprises 2-(4-fluorophenoxy)-N-[4-(1-hydroxy-1-methyl-ethyl)-benzyl]-nicotinamide or a pharmaceutically acceptable salt thereof; and wherein said swelling composition comprises about 35 and about 45% (w:w) sodium starch glycolate, about 35% and about 45% microcrystalline cellulose and about 10% and about 20% lactose; said drug layer comprises about 0.5 and about 10% of said drug, about 5% and about 10% sodium starch glycolate, about 30% and about 50% polyethylene oxide having a weight average molecular weight of about 200,000 and about 1,000,000, and about 30% and about 55% xylitol; and said coating comprises cellulose acetate and polyethylene glycol having a molecular weight (weight average) of between about 1,000 and about 10,000.

22. A method of treating disorders and conditions mediated by the PDE4D isozyme, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a PDE4D inhibitor, or a pharmaceutically acceptable salt thereof, in a controlled-release formulation of claim 3.

23. A method of claim 22, wherein said PDE4D inhibitor comprises (R)-2-[4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid, or a pharmaceutically acceptable salt thereof, or 2-(4-fluorophenoxy)-N-[4-(1-hydroxy-1-methyl-ethyl)-benzyl]-nicotinamide, or a pharmaceutically acceptable salt thereof.

24. A method of claim 22, wherein said disorders and conditions are selected from the group consisting of:

(a) inflammatory diseases and conditions selected from the group consisting of joint inflammation, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, inflammatory bowel disease, ulcerative colitis, chronic glomerulonephritis, dermatitis, and Crohn's Disease;

(b) respiratory diseases and conditions selected from the group consisting of asthma, acute respiratory distress syndrome, chronic obstructive pulmonary disease, bronchitis, chronic obstructive airway disease, and silicosis;

(c) infectious diseases and conditions selected from the group consisting of sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, fever and myalgias due to bacterial, viral or fungal infection, and influenza;

(d) immune diseases and conditions selected from the group consisting of autoimmune diabetes, systemic lupus erythematosis, graft v. host reaction, allograft rejections, multiple sclerosis, psoriasis, and allergic rhinitis; and

(e) other diseases and conditions selected from the group consisting of bone resorption diseases, reperfusion injury, cachexia secondary to infection or malignancy, cachexia secondary to human immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV), infection, or AIDS related complex (ARC), keloid formation, scar tissue formation, Type 1 diabetes mellitus, and leukemia.

25. A method of claim 24, wherein said disorders and conditions are selected from the group consisting of asthma, acute respiratory distress syndrome, chronic obstructive pulmonary disease, bronchitis, chronic obstructive airway disease, and silicosis.

26. A method of reducing PDE4D inhibitor treatment-induced nausea and/or emesis in a mammal which comprises administering said PDE4D inhibitor, or a

pharmaceutically acceptable salt thereof, to said mammal in the form of a controlled-release formulation of claim 3.

27. A method of claim 26, wherein said PDE4D inhibitor comprises (R)-2-[4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid, or a pharmaceutically acceptable salt thereof, or 2-(4-fluorophenoxy)-N-[4-(1-hydroxy-1-methyl-ethyl)-benzyl]-nicotinamide, or a pharmaceutically acceptable salt thereof.